



USAMRMC

United States Army Medical Research and Materiel Command Medical Systems Acquisitions

Adenovirus Vaccine Restoration

**Presentation to
Armed Forces Epidemiological
Board**

May 12, 2004

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**Vaccine Area Commodity Manager,
(Including Adenovirus Vaccine),**



Outline

- AFEB Letter from February Meeting
 - Specific actions taken to address points in letter.
- Schedule
- Milestones achieved since February Meeting
- Summary of 1997 clinical trial of previous vaccine done at WRAIR
- Acquisition Plan Risks
- Summary



Summary of AFEB concerns from February 2004 Meeting

4. Concern over the timeline, minimal contact with FDA, requirements, and lack of single high level responsible individual to assure timely re-acquisition.
5. Concern that DOD had not addressed the underlying causes of procurement system failure and make necessary changes.
6. DOD must provide the impetus for adenovirus vaccine.



Summary of AFEB recommendations from February Meeting

7. Recommendation:

- a. Appoint a high-level, single point of contact for this vaccine.
- b. Charge individual with responsibility to develop immediate and sustained interaction with FDA counterparts so that specific time-frames for vaccine acquisition can be established and to assure that barriers and obstacles can be overcome.
- c. Empower this individual to work with whomever else is necessary within the DOD to create a formal requirements document for adenovirus vaccine. The board would appreciate the opportunity to review such a document at its next meeting.



Actions taken to address AFEB recommendations from February Meeting

7. Recommendation:

- a. Appoint a high-level, single point of contact for this vaccine.
- *ASD(HA) briefed by CG, MRMC and Deputy for Acquisition*
- *ASD(HA) identified officer to provide oversight*
- *Product Manager and Deputy Product Manager identified*
 - *Formed Integrated Product Team and held first meeting*
 - *Drafted IPT charter*



Actions taken to address AFEB recommendations from February Meeting

- *Barr had met with FDA on 5 March 2003 to discuss plans for production facility*
- *Product Manager and Deputy Product Manager participated in pre-IND meeting (10 May 2004) with FDA, requested by Barr, to discuss adenovirus vaccine reacquisition effort. Numerous areas were discussed and clarified. (see below)*



Summary of FDA recommendations to Barr Laboratories and DOD representatives at 10 May 2004 meeting

- *Meeting was requested by Barr and chaired by their Director of Regulatory Affairs.*
- *FDA officials offered numerous suggestions regarding safety, manufacturing, immunogenicity, clinical trial design, and licensure considerations.*
- *Names of attendees will be provided immediately.*
- *FDA will provide minutes within 30 days.*

- *The following slides detail the suggestions/requests that were made.*



Regarding epidemiology, FDA

- *Requested update on epidemiology from 1999-2000 data in pre-IND package.*



Regarding general strategy, FDA

- accepted notion that this vaccine is a replacement of a similar, previously licensed vaccine.
- agreed that adenovirus 4 and 7 vaccines could be filed under a single IND and, presumably, license application.
- requested advance consultation on any study that will contribute to the licensure data package. Felt that study with old vaccine was not sufficient bridging study to allow them to approve vaccine on basis of safety and immunogenicity alone.
- wanted to know how DOD intends to use the vaccine (so information to support intended use could be sought for the label)
- did not feel that adequate data had been presented to support the argument that neutralizing antibody was a surrogate for protection.
 - Methods for neutralizing antibody testing varied and were not validated
 - Single available study was not convincing that a general principal had been established.



Regarding vaccine, FDA

- *stated that later transition to MRC-5 cells would require a new IND.*
 - *(PM requested collaboration from CBMS on obtaining MRC-5 cells)*
- *requested chromosomal spread to assure diploid nature of WI-38 cells.*
- *suggested type specific PCR to demonstrate lack of cross infection of vaccines.*
- *requested tracking pedigree of cells to assure no possibility of exposure to serum that might contain agent of BSE*



Regarding Safety, FDA

- *Requested old data on use of vaccine in women by military, particularly in any women who might have received vaccine while pregnant. (and what was the outcome?)*
- *Implied that military should seek any old data that might shed light on safety of vaccine.*
- *May request reproductive toxicity testing, but later in process. (Requested Barr's thoughts on reproductive toxicity).*
- *Will want post marketing surveillance data, particularly from female recipients.*
- *Requested current safety data on 1500 subjects*
- *Wanted to know how vaccine would be used in female trainees (e.g. after testing for pregnancy, if such testing is done before basic training).*



Regarding Clinical Development

- Asked for statistical basis for size of initial protocol with safety determination as a primary endpoint.
- Asked that spouses of subjects not be pregnant.
- Asked that female subjects not become pregnant for 3 months.
- Asked that subjects with history of GI surgery for the past year be excluded.
- Requested both throat and stool swabs in shedding studies.
- Requested 6 month verbal (by telephone) follow up of subjects to detect new medical conditions
- Suggested that we add cancer to list of conditions to ask about.
- Requested a stopping rule for the study.
- Suggested that we consider excluding former military .
- Requested a study that demonstrated efficacy, with a reasonable number of subjects (maybe 300 per arm) and a relatively easily identified case definition (hospitalization due to adenovirus infection).
- Adjust protocol to allow second dose if vomiting occurs within 2 hrs of dose.



Regarding Endpoint Assay, FDA

- *Suggested use of PRNT50 (instead of TCID50) type of assay for antibody testing for immunogenicity endpoint.*
- *Requested information relating old and new assays.*
- *Suggested manageable case definition for efficacy studies (e.g. febrile, acute respiratory infection with adenovirus present in throat culture.)*



AFEB Recommendation

- *MRMC Deputy for Acquisition requested appropriate requirements documents from AMEDD Center and School. Current status is that MRMC Liaison to AMEDD Center and School is working with staff there to generate general Initial Capabilities Document by 1 June. Subsequently, adenovirus vaccine specific Capability Production Document will be generated.*
- c. Empower this individual to work with whomever else is necessary within the DOD to create a formal requirements document for adenovirus vaccine. The board would appreciate the opportunity to review such a document at its next meeting.



Response to AFEB recommendations from February Meeting (cont'd)

8. Recommendation:
 - a. Make assays available for diagnosis of recruits in training camp medical facilities.
 - b. Develop and adapt antiviral treatment algorithms for individuals with severe adenovirus illness.
- *FDA website consulted on availability of FDA approved adenovirus diagnostic tests. Several assays are available.*
- *Dr. John Huggins at USAMRIID was consulted regarding anti-adenovirus drugs. Cidofovir has been evaluated, and may have some promise. (see: Kaneko H, et al. The cotton rat model for adenovirus ocular infection: antiviral activity of cidofovir., Antiviral Res. 2004 Jan;61(1):63-6.)*
- *No strategy for implementation of this recommendation has been adopted.*
- *Neither funding nor staff within the laboratory is currently available to address this recommendation.*
- *A plan will be prepared for presentation in the near future.*

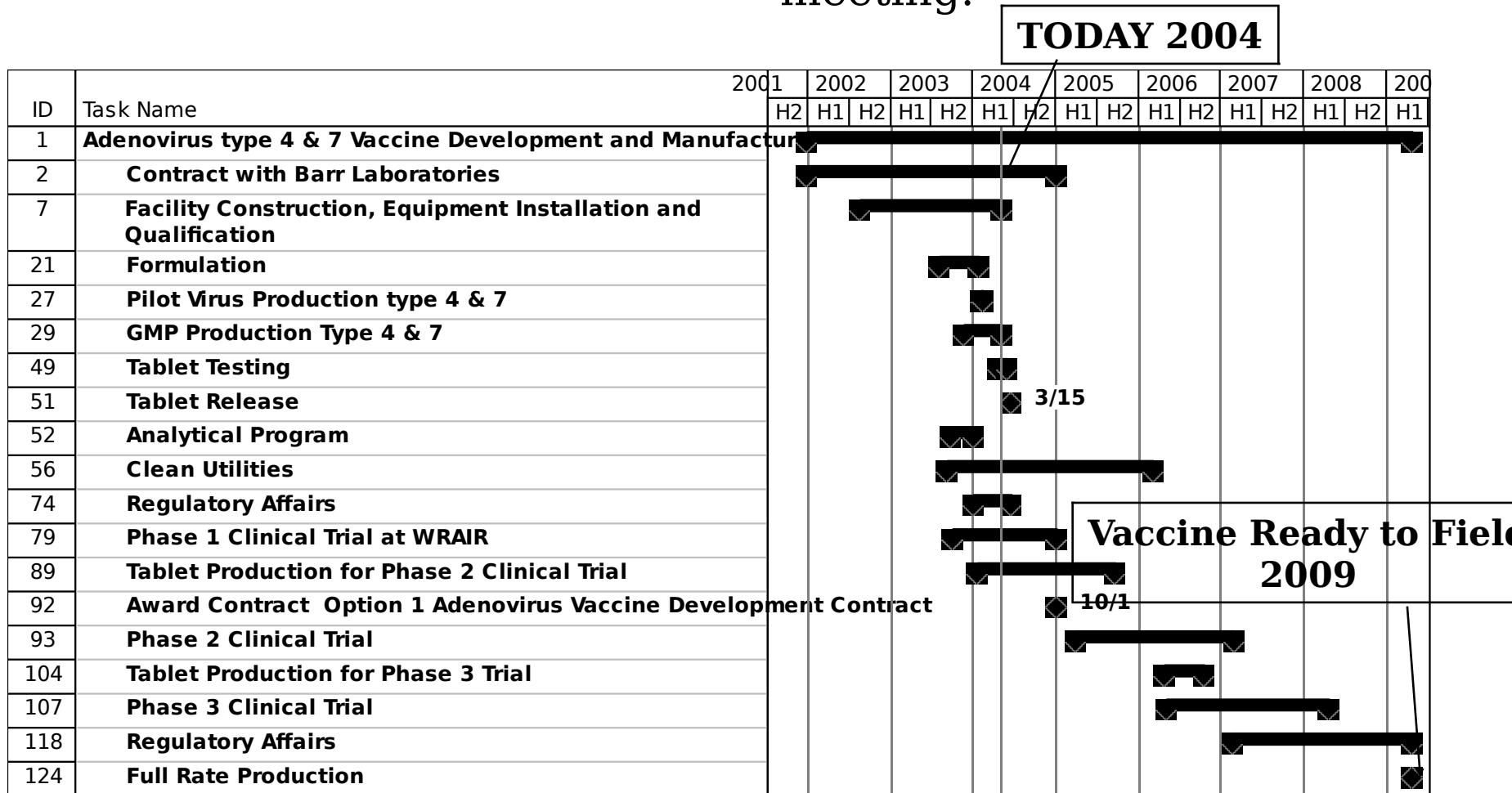


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Schedule

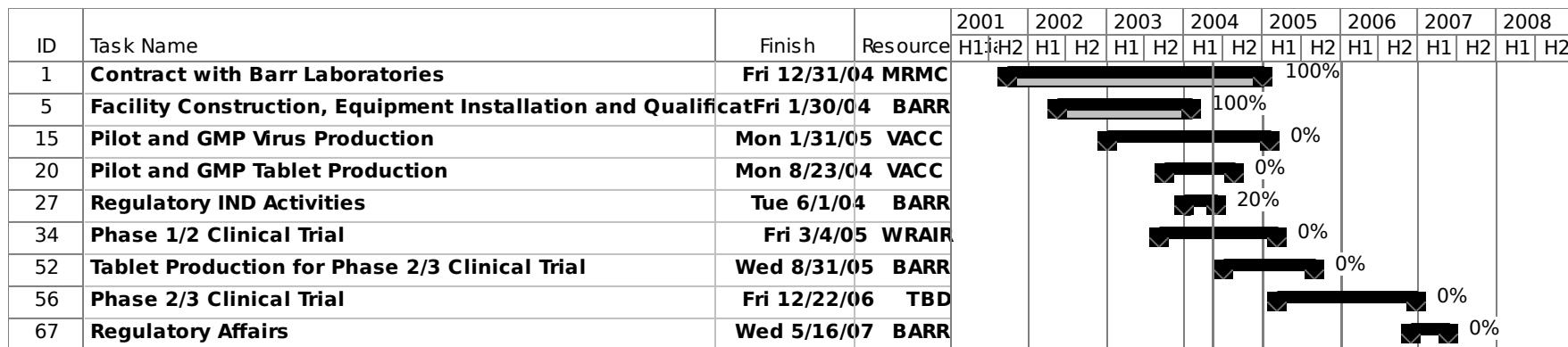


Schedule for Adenovirus Vaccine Restoration Presented at Feb 2004 AFEB meeting.





Revised (5/2004) Schedule for Adenovirus Vaccine Restoration



Subsequent slides expand plans for major components



Schedule for Facility Construction and Equipment Installation and Qualification

ID	Task Name	Finish	Resource	2001	2002	2003	2004	2005	2006	2007	2008
				H1	H2	H1	H2	H1	H2	H1	H2
5	Facility Construction, Equipment Installation and Qualification	Fri 1/30/04	BARR								
6	Tableting Facility	Fri 1/30/04	BARR								
7	Facility Construction	Tue 5/20/03									
8	Production Equipment Installed	Thu 8/28/03									
9	Extract Booth	Fri 1/30/04									
10	Freezers	Fri 1/30/04									
11	Equipment PQ & Process Validations	Wed 10/15/03									
12	Building Automation System BAS Validation	Fri 1/30/04									
13	Validation	Mon 12/1/03	ALAN								
14	Formulation	Wed 12/31/03	ALAN								



Schedule for Pilot and GMP Tablet Production

ID	Task Name	Finish	Resource	2001		2002		2003		2004		2005		2006		2007		2008	
				H1	H2														
20	Pilot and GMP Tablet Production	Mon 8/23/04	VACC																
21	Placebo Tablet Production (Pilot)	Wed 12/31/03																	
22	Virus Tablet Production	Mon 8/9/04	ANDY																
23	Pilot Virus Tablet Production	Fri 4/23/04																	
24	Testing	Wed 6/2/04																	
25	GMP Tablet Production	Mon 8/9/04																	
26	Product Release for Phase I	Mon 8/23/04																	



Schedule for IND filing activities

ID	Task Name	Finish	Resource	2001		2002		2003		2004		2005		2006		2007		2008	
				H1	H2														
27	Regulatory IND Activities	Tue 6/1/04	BARR																
28	Draft IND	Wed 3/24/04																	
29	Send pre-IND Letter	Thu 3/11/04																	
30	Submit pre-IND packet	Sat 4/10/04																	
31	Conduct pre-IND Meeting	Mon 5/10/04																	
32	Finalize IND	Mon 5/10/04	31																
33	File IND	Tue 6/1/04	32																



Schedule for Phase 1-2 Clinical Trial

ID	Task Name	Finish	Resource	2001		2002		2003		2004		2005		2006		2007		2008	
				H1	H2														
34	Phase 1/2 Clinical Trial	Fri 3/4/05 WRAIR																	
35	Protocol Preparation	Fri 4/30/04																	
36	Review and Approval	Fri 5/28/04 WRAIR																	
37	WRAIR Scientific Review	Fri 3/12/04																	
38	HSRRB Review	Fri 3/19/04																	
39	Review & approval of amendment using Ft. Sam Houston	Wed 3/31/04																	
40	Local IRB Review	Fri 5/14/04																	
41	USAMRAA Contract Modified for Human Use	Fri 5/28/04																	
42	HURC Protocol Review	Wed 12/3/03																	
43	Validation of microneut assay for volunteers	Wed 7/21/04																	
44	Validation of Taqman RT_PCR for quantitation of Adeno 4&7	Wed 7/21/04																	
45	Validation of isolation and identification assays ADV4&7 in throat tool	Wed 9/1/04																	
46	FPI / LPI (6mos treatment?)	Thu 9/30/04																	
47	Treatment	Tue 11/2/04																	
48	LPO	Wed 11/3/04																	
49	Conduct Assays	Fri 2/4/05																	
50	Data Analysis	Fri 12/17/04																	
51	Final Study Report	Fri 3/4/05																	



Schedule for Phase 2-3 Clinical Trial

ID	Task Name	Finish	Resource	2001		2002		2003		2004		2005		2006		2007		2008	
				H1	H2														
52	Tablet Production for Phase 2/3 Clinical Trial	Wed 8/31/05 BARR																	
53	Virus Production for Six Consistency Lots	Tue 5/31/05																	
54	Lyo. Validation	Thu 12/30/04																	
55	Tablet Production for Ph III at Barr	Wed 8/31/05																	
56	Phase 2/3 Clinical Trial	Fri 12/22/06 TBD																	
57	Protocol Preparation	Fri 3/18/05																	
58	Review and Approval	Fri 8/19/05																	
59	WRAIR Scientific Review	Fri 4/1/05																	
60	HSRRB Review	Fri 4/8/05																	
61	Review & Approval	Wed 4/20/05																	
62	Local IRB Review	Fri 5/13/05																	
63	USAMRAA Contract Modified for Human Use	Fri 8/19/05																	
64	FPI / LPO	Fri 9/29/06																	
65	Data Analysis	Fri 9/29/06																	
66	Final Study Report	Fri 12/22/06																	

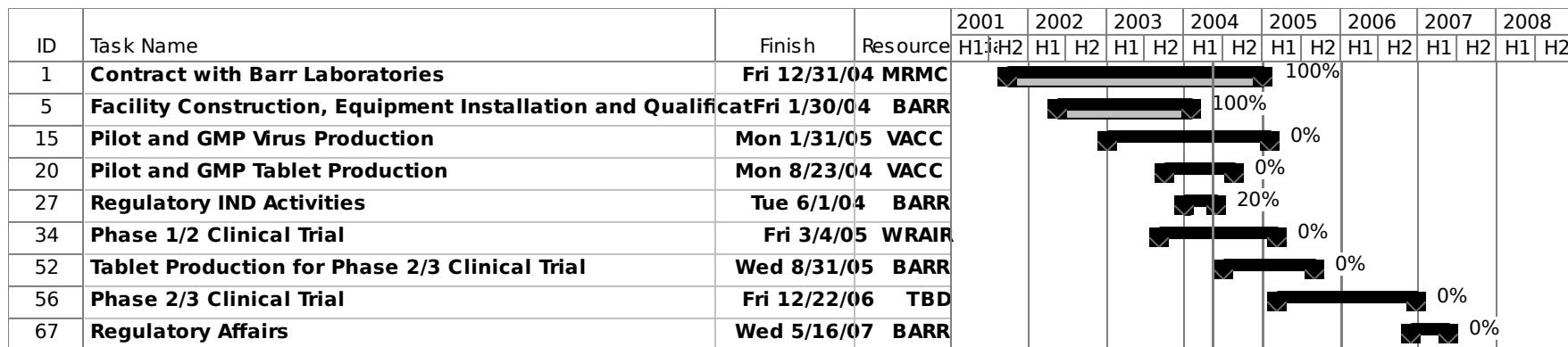


Schedule for Regulatory Affairs

ID	Task Name	Finish	Resource	2001	2002	2003	2004	2005	2006	2007	2008
				H1	H2	H1	H2	H1	H2	H1	H2
67	Regulatory Affairs	Wed 5/16/07	BARR								
68	BLA Package Preparation	Tue 5/1/07									
69	BLA Submission	Wed 5/16/07									



Overall Schedule for Adenovirus Vaccine Restoration





Milestones

- Received March 31st 2004 quarterly report from contractor
- Clinical trial (Phase I/II) protocol submitted (March 2004)
 - Completed HSRRB review and obtained approval for implementation. (date)
 - Study team from WRAIR visited Ft. Sam Houston to organize trial.
 - Study team from WRAIR visited Ft. Leonard Wood to identify study site for recruits.
 - Arranged smaller scale seroprevalence survey of prospective study population.
- Contracting issues
 - Modification put in place. Awaiting confirmation.
 - Option 2 exercised.
 - IND responsibility transferred by MRMC to Barr.
 - Identified minor contract changes that are needed.



Summary of Contractor's Quarterly Report (Through

31 March 2004)

- A. Bulk virus production at Q-One
- B. Formulation and Lyophilization at WRAIR
- C. Assay Development
- D. Tablet Production
- E. Clinical Trials
- F. DOD issues
- G. Financial issues



A. Bulk Virus Production

Master Virus Banks extensively tested and passed

- Sterility all required tests
- Mycoplasma
- Titer
- HBV
- HCV
- HIV-1
- HIV-2
- HTLV-1
- HTLV-2
- HHV-6
- HHV-7
- HHV-8
- HCMV
- SV40
- PERT
- In vivo
- Simian virus
- Mycobacteria
- AAV
- Identity
- Bovine
- Porcine
- Number of vials (447 type 4 and 465 type 7)



ADV-4 GMP Lots for Vaccine

- Production done with limited ~~duration~~ duration saved a 6-8 months.
- Production of ADV-4 GMP lot from October 2003 had acceptable titer.
- Filtration step lost little virus.
- ADV-4 GMP lot was transferred from Q-One to WRAIR for production of lyophilized, stabilized virus for further processing into tablets for the clinical trial.
- Following tests were completed on ADV 4 virus with satisfactory results:
 - Titer Bulk Harvest (10 exp 7.07 TCID50/ml)
 - Titer (Post Filtration) (10 exp 7.05 TCID50/ml)
 - Sterility
 - Mycoplasma
 - PERT
 - Identity
 - In vivo
 - Final Harvest Volume (480 ml)
- Control Cells
 - Hemadsorbing virus
 - In vitro
 - PERT



ADV-7 GMP Lots for Vaccine

- Replacement batch shipped to ~~Production~~ January 2004. Titer was good and sufficient virus was harvested to formulate and lyophilize virus for subsequent GMP production. The testing of the type 7 GMP lot has passed all tests as summarized below.
- Following tests were completed on ADV 7 virus with satisfactory results:
 - Titer Bulk Harvest (10 exp 7.34 TCID50/ml)
 - Titer (Post Filtration) (10 exp 6.9 TCID50/ml)
 - Sterility
 - Mycoplasma
 - PERT
 - Identity
 - In vivo
 - Final Harvest Volume (1444 ml)
- Control Cells
 - Hemadsorbing virus
 - In vitro
 - PERT



B. Formulation and Lyophilization at WRAIR

- GMP ADV-4
 - Single GMP production run of 2 Lyoguard trays containing 8,000 ADV-4 doses in total was produced and is being stored at WRAIR until shipment to the Barr Virginia facility for GMP Tablet production.
- GMP ADV-7
 - GMP ADV-7 lyophilization was successfully performed at WRAIR PBF in February 2004. A single production run of 5 trays containing sufficient virus to make 20,000 tablets was produced and is stored at WRAIR until shipment to Barr.



C. Assay

Development

- WRAIR will perform identity test by PCR.
 - Assay validation is ongoing
 - 352 swabs from environmental cleaning
 - Tested at WRAIR
 - Results indicate that current cleaning program successfully removes adenovirus to levels below those obtained by hydrogen peroxide.
- Assays for clinical trials
 - Neutralization test under development at WRAIR.
 - Protocol to obtain human sera for use in neutralization assay approved



C. Assay

Development

- Antisera for In Vitro Adventitious Agents
 - Serum required to neutralize virus
 - QS for current GMP lots and 2 additional lots.
 - New antisera program to be initiated in current year.
- Methods for Virus Inactivation
 - Conducted experiment to show that BioQuell vapor phase hydrogen peroxide system could inactivate ADV 4 and 7.
 - BioQuell contracted for decontamination services.



D. Tablet Production Facility

- ADV- 4
 - 1st pilot batch of ADV-4 tablets produced.
 - Virus titer did not change.
 - Bioreliance General Safety Test passed.
 - Acetone and ethanol contents were above the expected values.
 - Tablets failed disintegration test.
 - Testing of second pilot lot deferred until disintegration issue solved.
- ADV-7
 - Core tablet equipment malfunction delayed production.
 - Problem corrected.
 - 2 pilot batches of ADV 7 tablets are currently undergoing testing.
- Enteric Coating
 - Process uses ethanol and acetone to dissolve a polymer (CAP) used to coat tablets.
 - In coating pilot lots, found solvent content was too high, and tablets disintegrated too quickly.
 - Coating Protocol being modified.
- FDA GMP inspection April 5-14.
 - Did not include adenovirus tablet facility, but did include Barr Quality Systems.
 - Barr pleased with FDA inspection results.



E. Clinical Trials

- Pre IND meeting 10 May 2004 (see earlier slides.)
- Plan:
 - Two trials proposed:
 - AMEDD C&S 60 volunteers: enlisted soldiers in advanced training (91W)
 - Ft. Leonard Wood: 1500 volunteers (Officers Advanced School)
 - Sites visited.
 - Commanders are very supportive.
 - Resources identified
 - Seroprevalence study will be conducted at Ft. Sam to determine prevalence of antibody in 91W population.
 - Plan approved for implementation at WRAIR.
 - FDA has requested efficacy testing, and this trial will be factored into above plan.



F. DoD Issues

- AFEB and ASD(HA) interest are noted.
- Scope change proposal discussed on April 14 2004. Barr asked for \$5.2 M above original contract for items mostly related to insufficient records from Wyeth.
- Option 1. Contract Mod 10 exercised option 1 which covers both Phase II and III Clinical Trials.
- FY03 billing rates. Contractor was unfamiliar with government procedures for billing for overhead, and remedies are being negotiated.



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Results of Trial of Original Adenovirus Vaccine Conducted by WRAIR in 1997



Characterization of serologic and virologic responses of healthy, adult volunteers to the licensed, live adenovirus vaccines

Study conducted by COL Robert Kuschner
Data provided by Dr. Wellington Sun



Trial of Previously Licensed Wyeth Adenovirus Vaccine

- Investigator: COL Robert Kuschner
- Conducted: 1997
- Vaccines (Both vaccines administered orally to all subjects)
 - Adenovirus 4 FDA Approved Vaccine
 - Adenovirus 7 FDA Approved Vaccine
- Purpose of trial: To provide benchmark for comparison with replacement vaccine
- Location: WRAIR
- Subjects: Healthy adults
- Endpoints:
 - Virus neutralizing antibody
 - Reported symptoms



Results of trial

- Subjects
 - 40 enrolled
 - 4 developed antibody between the time of screening and the time of vaccine administration.
 - 1 lost to followup.
 - 35 analyzed.
 - Antibody status before immunization:
 - Both 4 and 7: 0
 - Neither 4 nor 7: 8
 - 4 only: 5
 - 7 only: 22
 - Total starting without type 4 antibody: 30
 - Total starting without type 7 antibody: 13



Seroconverters following immunization with Wyeth

- Adenovirus 4 Vaccine
 - Seronegative (SN*<2): n=30
 - Seroconverters: 27 (90%)
- Adenovirus 7
 - Seronegative (SN(2)): n=13
 - Seroconverters: 13 (100%)

*SN=Serum Neutralizing Antibodies



Distribution of adenovirus antibody at day 28 following oral immunization

	Ratio of day 28 titer:day 0 titer (all were <2)	<2	<4	<8	<16	<32
	Indeterminate					
A 4	3	5	10	2	8	2
A 7	0	1	0	0	2	10



Adenovirus excretion following immunization

	Fecal Culture Positive	Throat Culture Positive
A 4	30/30	0/30
A 7	13/13	0/13

Samples were cultured on days 3, 7, 10, 14, 21, 28



Adverse events following immunization with previously licensed Wyeth adenovirus vaccine

	N=35 Subjects
Feverishness	3
Nasal Congestion	12
Sore Throat	6
Cough	6
Vomiting	1
Diarrhea	8

Total of mild,
moderate or
severe symptoms
recorded in
volunteer diaries.



Adenovirus Vaccine Reacquisition Program Risks

- Permanent virus production facility has yet to be identified.
- Clinical trial program
 - Efficacy study requested by FDA may increase timeline and costs.
 - Initial clinical trial
 - Protocol amendments from FDA will require expedited IRB review to avoid delay onset of first trial.
 - If September start date cannot be met, start will be postponed until January 2005.
 - Clinical teams for later studies not yet identified.
- Serological testing
 - Serological endpoint test remains to be validated.
 - Site to perform large number of tests remains to be identified.
- Reproductive toxicity studies may be required.



Additional Acquisition System Steps

- Obtain Capability Production Document
- Complete Product Manager's Charter
- Complete Integrated Product Team charter
- Complete Test Plan
- Hold Milestone Review (? C)
- Present Test Plan to Milestone Decision Authority for Approval
- Assure adequate future budget authority



How can the AFEB

- Continue to function as A&P (IA) Overarching Integrated Product Team to track vaccine availability, sustainment, and restoration.
- Consider what policy for use of this vaccine AFEB would recommend.
- Consider recommendations regarding Treatment use of Investigational New Drug once all required studies have been completed. 21 CFR 312.34 requires that the treatment is for a serious disease, that there be no satisfactory alternative, that the drug is under investigation in a controlled clinical trial or all clinical trials have been completed and the sponsor is actively pursuing licensure.



Summa

- Adenovirus vaccine acquisition effort is advancing towards the goal.
- MRMC is molding program into a model acquisition effort.
- Contractor is making progress.
- FDA has provided detailed guidance.
- Many problems remain to be solved, but no unsurmountable obstacle is presently foreseen.



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The Adenovirus Vaccine
Re-acquisition program is
NOT business as usual.



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QUESTIONS?

